

General

Guideline Title

Lyme disease.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Lyme disease. London (UK): National Institute for Health and Care Excellence (NICE); 2018 Apr 11. 42 p. (NICE guideline; no. 95).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report [Clinical Practice Guidelines We Can Trust](#).

■■■■= Poor ■■■■= Fair ■■■■= Good ■■■■= Very Good ■■■■= Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source
■■■■	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
YES	Multidisciplinary Group
YES	Methodologist Involvement
■■■■	Patient and Public Perspectives

	Use of a Systematic Review of Evidence
■■■■■	Search Strategy
■■■■■	Study Selection
■■■■■	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
■■■■■	Grading the Quality or Strength of Evidence
■■■■■	Benefits and Harms of Recommendations
■■■■■	Evidence Summary Supporting Recommendations
■■■■■	Rating the Strength of Recommendations
■■■■■	Specific and Unambiguous Articulation of Recommendations
■■■■■	External Review
■■■■■	Updating

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Guideline Centre on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the evidence reviews for this guidance.

The wording used in the recommendations in this guideline (for example words such as 'offer' and 'consider') denotes the certainty with which the recommendation is made (the strength of the recommendation) and is defined at the end of the "Major Recommendations" field.

Awareness of Lyme Disease

Be aware that:

The bacteria that cause Lyme disease are transmitted by the bite of an infected tick
 Ticks are mainly found in grassy and wooded areas, including urban gardens and parks
 Tick bites may not always be noticed
 Infected ticks are found throughout the UK and Ireland, and although some areas appear to have a higher prevalence of infected ticks, prevalence data are incomplete
 Particularly high-risk areas are the South of England and Scottish Highlands but infection can occur in many areas
 Lyme disease may be more prevalent in parts of central, eastern and northern Europe (including Scandinavia) and parts of Asia, the US and Canada.

Be aware that most tick bites do not transmit Lyme disease and that prompt, correct removal of the tick reduces the risk of transmission.

Give people advice about:

Where ticks are commonly found (such as grassy and wooded areas, including urban gardens and parks)

The importance of prompt, correct tick removal and how to do this (see the [Public Health England Web site](#) for information on removing ticks)

Covering exposed skin and using insect repellents that protect against ticks

How to check themselves and their children for ticks on the skin

Sources of information on Lyme disease, such as Public Health England, and organisations providing information and support, such as patient charities.

To find out why the committee made the recommendations on awareness of Lyme disease and how they might affect practice, see [rationale and impact](#) .

Diagnosis

Clinical Assessment

Diagnose Lyme disease in people with erythema migrans, a red rash that:

Increases in size and may sometimes have a central clearing

Is not usually itchy, hot or painful

Usually becomes visible from 1 to 4 weeks (but can appear from 3 days to 3 months) after a tick bite and lasts for several weeks

Is usually at the site of a tick bite.

NICE has also produced a resource with images showing erythema migrans (see the "Availability of Companion Documents" field).

Be aware that a rash, which is not erythema migrans, can develop as a reaction to a tick bite that:

Usually develops and recedes during 48 hours from the time of the tick bite

Is more likely than erythema migrans to be hot, itchy or painful

May be caused by an inflammatory reaction or infection with a common skin pathogen.

Consider the possibility of Lyme disease in people presenting with several of the following symptoms, because Lyme disease is a possible but uncommon cause of:

Fever and sweats

Swollen glands

Malaise

Fatigue

Neck pain or stiffness

Migratory joint or muscle aches and pain

Cognitive impairment, such as memory problems and difficulty concentrating (sometimes described as 'brain fog')

Headache

Paraesthesia.

Consider the possibility of Lyme disease in people presenting with symptoms and signs relating to 1 or more organ systems (focal symptoms) because Lyme disease is a possible but uncommon cause of:

Neurological symptoms, such as facial palsy or other unexplained cranial nerve palsies, meningitis, mononeuritis multiplex or other unexplained radiculopathy; or rarely encephalitis, neuropsychiatric presentations or unexplained white matter changes on brain imaging

Inflammatory arthritis affecting 1 or more joints that may be fluctuating and migratory cardiac problems, such as heart block or pericarditis

Eye symptoms, such as uveitis or keratitis

Skin rashes such as acrodermatitis chronica atrophicans or lymphocytoma.

If a person presents with symptoms that suggest the possibility of Lyme disease, explore how long the person has had symptoms and their history of possible tick exposure, for example, ask about:

- Activities that might have exposed them to ticks
- Travel to areas where Lyme disease is known to be highly prevalent.

Do not rule out the possibility of Lyme disease in people with symptoms but no clear history of tick exposure.

Do not diagnose Lyme disease in people without symptoms, even if they have had a tick bite.

Be cautious about diagnosing Lyme disease in people without a supportive history or positive serological testing because of the risk of:

- Missing an alternative diagnosis
- Providing inappropriate treatment.

Follow usual clinical practice to manage symptoms, for example, pain relief for headaches or muscle pain, in people being assessed for Lyme disease.

Take into account that people with Lyme disease may have symptoms of cognitive impairment and may have difficulty explaining their symptoms. For adults, follow the recommendations in NICE's guideline on [patient experience in adult NHS services](#) .

To find out why the committee made the recommendations on clinical assessment and how they might affect practice, see [rationale and impact](#) .

Laboratory Investigations to Support Diagnosis

NICE has also produced a visual summary of the recommendations on testing for Lyme disease (see the "Clinical Algorithm" field).

Diagnose and treat Lyme disease without laboratory testing in people with erythema migrans.

Use a combination of clinical presentation and laboratory testing to guide diagnosis and treatment in people without erythema migrans. Do not rule out diagnosis if tests are negative but there is high clinical suspicion of Lyme disease.

If there is a clinical suspicion of Lyme disease in people without erythema migrans:

- Offer an enzyme-linked immunosorbent assay (ELISA) test for Lyme disease and
- Consider starting treatment with antibiotics while waiting for the results if there is a high clinical suspicion.

Test for both IgM and IgG antibodies using ELISAs based on purified or recombinant antigens derived from the VlsE protein or its IR6 domain peptide (such as C6 ELISA).

If the ELISA is positive or equivocal:

- Perform an immunoblot test for Lyme disease and
- Consider starting treatment with antibiotics while waiting for the results if there is a high clinical suspicion of Lyme disease.

If the ELISA for Lyme disease is negative and the person still has symptoms, review their history and symptoms, and think about the possibility of an alternative diagnosis.

If Lyme disease is still suspected in people with a negative ELISA who were tested within 4 weeks from symptom onset, repeat the ELISA 4 to 6 weeks after the first ELISA test.

If Lyme disease is still suspected in people with a negative ELISA who have had symptoms for 12 weeks or more, perform an immunoblot test.

Diagnose Lyme disease in people with symptoms of Lyme disease and a positive immunoblot test.

If the immunoblot test for Lyme disease is negative (regardless of the ELISA result) but symptoms persist, consider a discussion with or referral to a specialist, to:

- Review whether further tests may be needed for suspected Lyme disease, for example, synovial fluid aspirate or biopsy, or lumbar puncture for cerebrospinal fluid analysis or
- Consider alternative diagnoses (both infectious, including other tick-borne diseases, and non-infectious diseases).

Choose a specialist appropriate for the person's history or symptoms, for example, an adult or paediatric infection specialist, rheumatologist or neurologist.

If the immunoblot test for Lyme disease is negative and symptoms have resolved, explain to the person that no treatment is required.

Carry out tests for Lyme disease only at laboratories that:

- Are accredited by the UK accreditation service (UKAS) and
- Use validated tests (validation should include published evidence on the test methodology, its relation to Lyme disease and independent reports of performance) and
- Participate in a formal external quality assurance programme.

Do not routinely diagnose Lyme disease based only on tests done outside the National Health Service (NHS), unless the laboratory used is accredited, participates in formal external quality assurance programmes and uses validated tests (see next recommendation). If there is any doubt about tests:

- Review the person's clinical presentation and
- Carry out testing again using a UKAS-accredited laboratory and/or seek advice from a national reference laboratory.

To find out why the committee made the recommendations on laboratory investigations and how they might affect practice, see [rationale and impact](#) .

Information for People Being Tested for Lyme Disease

Tell people that tests for Lyme disease have limitations. Explain that both false-positive and false-negative results can occur and what this means.

Explain to people that most tests for Lyme disease assess for the presence of antibodies and that the accuracy of tests may be reduced if:

- Testing is carried out too early (before antibodies have developed)
- The person has reduced immunity, for example, people on immunosuppressant treatments, which might affect the development of antibodies.

Advise people that tests from non-UKAS laboratories may not have been fully evaluated to diagnose Lyme disease.

Explain to people that:

- The symptoms and signs associated with Lyme disease overlap with those of other conditions
- They will be assessed for alternative diagnoses if their tests are negative and their symptoms have not resolved
- Symptoms such as tiredness, headache and muscle pain are common, and a specific medical cause is often not found.

To find out why the committee made the recommendations on information, see [rationale and impact](#) .

Management

Emergency Referral

Follow usual clinical practice for emergency referrals, for example, in people with symptoms that suggest central nervous system infection, uveitis or cardiac complications such as complete heart block, even if Lyme disease is suspected.

Specialist Advice

Discuss the diagnosis and management of Lyme disease in children and young people under 18 years with a specialist, unless they have a single erythema migrans lesion and no other symptoms. Choose a specialist appropriate for the child or young person's symptoms dependent on availability, for example, a paediatrician, paediatric infectious disease specialist or a paediatric neurologist.

If an adult with Lyme disease has focal symptoms, consider a discussion with or referral to a specialist, without delaying treatment. Choose a specialist appropriate for the person's symptoms, for example, an adult infection specialist, rheumatologist or neurologist.

To find out why the committee made the recommendations on emergency referral and specialist advice and how they might affect practice, see [rationale and impact](#) .

Antibiotic Treatment

For adults and young people (aged 12 and over) diagnosed with Lyme disease, offer antibiotic treatment according to their symptoms as described in Table 1 below.

For children (under 12) diagnosed with Lyme disease, offer antibiotic treatment according to their symptoms as described in Table 2 below.

Ask women (including young women under 18) if they might be pregnant before offering antibiotic treatment for Lyme disease (see recommendation below on treatment in pregnancy).

If symptoms worsen during treatment for Lyme disease, assess for an allergic reaction to the antibiotic. Be aware that a Jarisch–Herxheimer reaction may cause an exacerbation of symptoms but does not usually warrant stopping treatment.

Consider clinical review during or after treatment for Lyme disease to assess for possible side effects and response to treatment.

Table 1. Antibiotic Treatment for Lyme Disease in Adults and Young People (Aged 12 and Over) According to Symptoms^a

Symptoms	Treatment	First Alternative	Second Alternative
Lyme Disease Without Focal Symptoms			
Erythema migrans and/or Non-focal symptoms	Oral doxycycline: 100 mg twice per day or 200 mg once per day for 21 days	Oral amoxicillin: 1 g 3 times per day for 21 days	Oral azithromycin ^b : 500 mg daily for 17 days
Lyme Disease with Focal Symptoms			
Lyme disease affecting the cranial nerves or peripheral nervous system	Oral doxycycline: 100 mg twice per day or 200 mg once per day for 21 days	Oral amoxicillin: 1 g 3 times per day for 21 days	—
Lyme disease affecting the central nervous system	Intravenous ceftriaxone: 2 g twice per day or 4 g once per day for 21 days (when an oral switch is being considered, use doxycycline)	Oral doxycycline: 200 mg twice per day or 400 mg once per day for 21 days	—
Lyme disease arthritis	Oral doxycycline: 100 mg twice per day or 200 mg once per day for 28	Oral amoxicillin: 1 g 3 times per day	Intravenous ceftriaxone:

Symptoms	Treatment	First Alternative	Second Alternative
Acrodermatitis chronica atrophicans	days	for 28 days	2 g once per day for 28 days
Lyme carditis ^b	Oral doxycycline: 100 mg twice per day or 200 mg once per day for 21 days	Intravenous ceftriaxone: 2 g once per day for 21 days	—
Lyme carditis and haemodynamically unstable	Intravenous ceftriaxone: 2 g once per day for 21 days (when an oral switch is being considered, use doxycycline)	—	—

^aFor Lyme disease suspected during pregnancy, use appropriate antibiotics for stage of pregnancy.

^bDo not use azithromycin to treat people with cardiac abnormalities associated with Lyme disease because of its effect on QT interval.

Table 2. Antibiotic Treatment for Lyme Disease in Children (Under 12) According to Symptoms^{a,b,c}

Symptoms	Age	Treatment	First Alternative	Second Alternative
Lyme Disease Without Focal Symptoms				
Erythema migrans and/or Non-focal symptoms	9–12 years	Oral doxycycline ^a for children under 45 kg: 5 mg/kg in 2 divided doses on day 1 followed by 2.5 mg/kg daily in 1 or 2 divided doses for a total of 21 days For severe infections, up to 5 mg/kg daily for 21 days	Oral amoxicillin for children 33 kg and under: 30 mg/kg 3 times per day for 21 days	Oral azithromycin ^{d,e} for children 50 kg and under: 10 mg/kg daily for 17 days
	Under 9	Oral amoxicillin for children 33 kg and under: 30 mg/kg 3 times per day for 21 days	Oral azithromycin ^{d,e} for children 50 kg and under: 10 mg/kg daily for 17 days	—
Lyme Disease with Focal Symptoms				
Lyme disease affecting the cranial nerves or peripheral nervous system	9–12 years	Oral doxycycline ^a for children under 45 kg: 5 mg/kg in 2 divided doses on day 1 followed by 2.5 mg/kg daily in 1 or 2 divided doses for a total of 21 days For severe infections, up to 5 mg/kg daily for 21 days	Oral amoxicillin for children 33 kg and under: 30 mg/kg 3 times per day for 21 days	—
	Under 9	Oral amoxicillin for children 33 kg and under: 30 mg/kg 3 times per day for 21 days	—	—
Lyme disease affecting the central nervous system	9–12 years	Intravenous ceftriaxone for children 50 kg and under: 80 mg/kg once per day for 21 days	Oral doxycycline ^a for children under 45 kg: 5 mg/kg in 2 divided doses on day 1 followed by 2.5 mg/kg daily in 1 or 2 divided doses for a total of 21 days For severe infections, up to 5 mg/kg daily	—
	Under 9	Intravenous ceftriaxone for children 50 kg and	—	—

Symptoms	Age	Treatment under: 80 mg/kg once per day for 21 days	First Alternative	Second Alternative
Lyme arthritis or Acrodermatitis chronica atrophicans	9–12 years	Oral doxycycline ^a for children under 45 kg: 5 mg/kg in 2 divided doses on day 1 followed by 2.5 mg/kg daily in 1 or 2 divided doses for a total of 28 days For severe infections, up to 5 mg/kg daily for 21 days	Oral amoxicillin for children 33 kg and under: 30 mg/kg 3 times per day 28 days	Intravenous ceftriaxone for children 50 kg and under: 80 mg/kg once per day for 28 days
	Under 9	Oral amoxicillin for children, 33 kg and under: 30 mg/kg 3 times per day for 28 days	Intravenous ceftriaxone for children 50 kg and under: 80 mg/kg once per day for 28 days	—
Lyme carditis (both haemodynamically stable and unstable) ^e	9–12 years	Oral doxycycline ^a for children under 45 kg: 5 mg/kg in 2 divided doses on day 1 followed by 2.5 mg/kg daily in 1 or 2 divided doses for a total of 21 days For severe infections, up to 5 mg/kg daily for 21 days	Intravenous ceftriaxone for children 50 kg and under: 80 mg/kg once per day for 21 days	—
	Under 9	Intravenous ceftriaxone for children 50 kg and under: 80 mg/kg once per day for 21 days	—	—

^aAt the time of publication (April 2018), doxycycline did not have a UK marketing authorisation for this indication in children under 12 years and is contraindicated. The use of doxycycline for children aged 9 years and above in infections where doxycycline is considered first line in adult practice is accepted specialist practice. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#) for further information.

^bDiscuss management of Lyme disease in children and young people with a specialist, unless they have a single erythema migrans lesion with no other symptoms; see "Specialist Advice" above.

^cChildren weighing more than the amounts specified should be treated according to Table 1.

^dAt the time of publication (April 2018), azithromycin did not have a UK marketing authorisation for this indication in children under 12 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#) for further information.

^eDo not use azithromycin to treat people with cardiac abnormalities associated with Lyme disease because of its effect on QT interval.

To find out why the committee made the recommendations on antibiotic treatment and how they might affect practice, see [rationale and impact](#) .

Ongoing Symptoms After a Course of Antibiotics

If symptoms that may be related to Lyme disease persist, do not continue to improve or worsen after antibiotic treatment, review the person's history and symptoms to explore:

Possible alternative causes of the symptoms

If re-infection may have occurred

If treatment may have failed

Details of any previous treatment, including whether the course of antibiotics was completed without interruption

If symptoms may be related to organ damage caused by Lyme disease, for example, nerve palsy.

If the person's history suggests re-infection, offer antibiotic treatment for Lyme disease according to their

symptoms (see Tables 1 and 2).

Consider a second course of antibiotics for people with ongoing symptoms if treatment may have failed. Use an alternative antibiotic to the initial course, for example, for adults with Lyme disease and arthritis, offer amoxicillin if the person has completed an initial course of doxycycline.

If a person has ongoing symptoms following 2 completed courses of antibiotics for Lyme disease:

- Do not routinely offer further antibiotics and
- Consider discussion with a national reference laboratory or discussion or referral to a specialist as outlined in a previous recommendation.

Explain to people with ongoing symptoms following antibiotic treatment for Lyme disease that:

- Continuing symptoms may not mean they still have an active infection
- Symptoms of Lyme disease may take months or years to resolve even after treatment
- Some symptoms may be a consequence of permanent damage from infection
- There is no test to assess for active infection and an alternative diagnosis may explain their symptoms.

To find out why the committee made the recommendations on ongoing symptoms after a course of antibiotics and how they might affect practice, see [rationale and impact](#) .

Non-antibiotic Management of Ongoing Symptoms

Offer regular clinical review and reassessment to people with ongoing symptoms, including people who have no confirmed diagnosis.

Explore any ongoing symptoms with the person and offer additional treatment if needed following usual clinical practice.

Be alert to the possibility of symptoms related to Lyme disease that may need assessment and management, including:

- Chronic pain
- Depression and anxiety (see NICE's guideline on common mental health problems)
- Fatigue
- Sleep disturbance.

Support people who have ongoing symptoms after treatment for Lyme disease by:

- Encouraging and helping them to access additional services, including referring to adult social care for a care and support needs assessment, if they would benefit from these
- Communicating with children and families' social care, schools and higher education, and employers about the person's need for a gradual return to activities, if relevant.

To find out why the committee made the recommendations on non-antibiotic management of ongoing symptoms and how they might affect practice, see [rationale and impact](#) .

Management for Women with Lyme Disease During Pregnancy and Their Babies

Assess and diagnose Lyme disease during pregnancy in the same way as for people who are not pregnant. Treat Lyme disease in pregnant women using appropriate antibiotics for the stage of pregnancy (see the British National Formulary [BNF] for more information on antibiotics during pregnancy).

Tell women with Lyme disease during pregnancy that they are unlikely to pass the infection to their baby and emphasise the importance of completing the full course of antibiotic treatment.

Advise women who had Lyme disease during pregnancy to tell this to their healthcare professional if they have any concerns about their baby. In this situation, healthcare professionals should discuss the history with a paediatric infectious disease specialist and seek advice on what investigations to perform.

Start treatment for Lyme disease under specialist care for babies of women treated for Lyme disease during pregnancy if the baby has IgM antibodies specific for Lyme disease or there is any suspicion the baby may be infected.

To find out why the committee made the recommendations on management for women with Lyme disease during pregnancy and their babies and how they might affect practice, see [rationale and impact](#) .

Information for People with Lyme Disease

Explain to people diagnosed with Lyme disease that:

- Lyme disease is a bacterial infection treated with antibiotics
- Most people recover completely
- Prompt antibiotic treatment reduces the risk of further symptoms developing and increases the chance of complete recovery
- It may take time to get better, but their symptoms should continue to improve in the months after antibiotic treatment
- They may need additional treatment for symptom relief.

Tell people who are starting antibiotics for Lyme disease that some people may have a Jarisch-Herxheimer reaction to treatment. Explain that:

- This causes a worsening of symptoms early in treatment
- It can happen when large numbers of bacteria in the body are killed
- It does not happen to everyone treated for Lyme disease
- They should contact their doctor and keep taking their antibiotics if their symptoms worsen.

Advise people with Lyme disease to talk to their doctor if their symptoms have not improved or if symptoms return after completing treatment.

Explain to people with Lyme disease that infection does not give them lifelong immunity and that it is possible for them to be re-infected and develop Lyme disease again.

To find out why the committee made the recommendations on information, see [rationale and impact](#) .

Definitions

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Committee (GC) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GC is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision.

Interventions That Must (or Must Not) Be Used

The GC usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally they use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GC uses 'offer' (and similar words such as 'refer' or 'advise') when they are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. They use similar forms of words (for example, 'Do not offer...') when they are confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GC uses 'consider' when they are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Clinical Algorithm(s)

A visual summary titled "Lyme disease: laboratory investigations and diagnosis" is provided on the [National Institute for Health and Care Excellence \(NICE\) Web site](#) .

In addition, a NICE pathway titled "Lyme disease overview" is provided on the [NICE Web site](#) .

Scope

Disease/Condition(s)

Lyme disease

Note: This guideline does not cover the diagnosis and management of other tick-borne infections or the prevention of Lyme disease.

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Family Practice

Infectious Diseases

Internal Medicine

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Patients

Physician Assistants

Physicians

Public Health Departments

Guideline Objective(s)

To raise awareness of when Lyme disease should be suspected and to ensure that people with suspected Lyme disease are given early and consistent treatment

Target Population

Adults, young people and children with suspected or confirmed Lyme disease

Interventions and Practices Considered

1. Awareness of Lyme disease
2. Diagnosis
 - Clinical assessment
 - Laboratory investigations
 - Information for people being tested for Lyme disease
3. Management
 - Emergency referral
 - Specialist advice
 - Antibiotic treatment
 - Treatment of ongoing symptoms (antibiotic and non-antibiotic)
 - Management of pregnant women and their babies
4. Information for people with Lyme disease

Major Outcomes Considered

- Incidence and prevalence of Lyme disease
- Sensitivity, specificity, positive predictive value, negative predictive value, and receiver operating characteristic (ROC) curve or area under curve (AUC) of tests
- Quality of life
- Cure (resolution of symptoms, including erythema migrans [EM])
- Reduction of symptoms
- Symptom relapse
- Adverse events
- Person-to-person transmission

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Guideline Centre on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the evidence reviews for this guidance.

Developing the Review Questions and Outcomes

Review questions were developed using a PICO framework (population, intervention, comparison and outcome) for intervention reviews; using a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy; and using a framework of population, setting and context for qualitative reviews.

The review questions on the transmission and incidence of Lyme disease were developed using a framework of population, target condition and measures of probability of occurrence, that is, legitimate incidence, prevalence or transmission risk estimates.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the guideline committee. The review questions were drafted by the National Guideline Centre technical team and refined and validated by the committee. The questions were based on the key clinical areas identified in the scope.

A total of 15 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions except for the question on the awareness of Lyme disease. The recommendations for raising awareness of Lyme disease were based on discussions, consensus and expert opinion of the committee and were also informed by other review questions. The committee agreed that there was no published evidence that could inform these recommendations.

The evidence included in the review chapter on the management of persistent symptoms was identified through the review on the management of non-specific symptoms. The committee agreed that the evidence on persistent symptoms associated with Lyme disease should be separated out because the study populations represented a different patient group seen in clinical practice. No separate review was undertaken for the management of persistent symptoms associated with Lyme disease as the committee agreed that treatment failure and duration of symptoms should be considered as part of each management review.

Searching for Evidence

Clinical and Health Economic Literature Searches

The full search strategy including population terms, intervention terms, study types applied, the databases searched and the years covered can be found in Appendix B of each evidence review report. Systematic literature searches were undertaken to identify all published clinical and health economic evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual 2014 (see the "Availability of Companion Documents" field). Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. An exclusion filter can be applied to remove certain study designs and publication types by using the Boolean operator 'NOT'. Studies published in languages other than English were not reviewed, where possible searches were restricted to English language. All searches were updated on 3 July 2017. Papers published or added to databases after this date were not considered. If new evidence falls outside of the timeframe for the guideline searches, for example, from stakeholder comments, the impact on the guideline will be considered, and any further action agreed between the developer and NICE staff with a quality assurance role.

Prior to running, searches were quality assured using different approaches. Medline search strategies were checked by a second information specialist before being run. Searches were crosschecked with reference lists of highly relevant papers, searches in other systematic reviews analysed, and committee members requested to highlight any additional studies they were aware of.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria in the protocols.

During the scoping stage, a search was conducted for guidelines and reports on the Web sites listed below from organisations relevant to the topic.

Guidelines International Network database (www.g-i-n.net)
National Guideline Clearinghouse (www.guideline.gov)
National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
National Health Service (NHS) Evidence Search (www.evidence.nhs.uk).

Searching for unpublished literature was not undertaken. The National Guideline Centre and NICE do not have access to drug manufacturers' unpublished clinical trial results, so the clinical evidence the committee considered for pharmaceutical interventions may be different from that the Medicines and Healthcare products Regulatory Agency (MHRA) and European Medicines Agency considered for the purposes of licensing and safety regulation.

Identifying Evidence of Effectiveness

Research fellows conducted the tasks listed below:

Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
Reviewed full papers against prespecified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population, and reported on outcomes of interest (review protocols are included in an appendix to each of the evidence reports).

Inclusion and Exclusion Criteria

The inclusion and exclusion of studies was based on the criteria defined in the review protocols, which can be found in an appendix to each of the evidence reports. Excluded studies (with the reasons for their exclusion) are listed in another appendix to each of the evidence reports. The committee was consulted about any uncertainty regarding inclusion or exclusion.

The key population inclusion criterion was:

People of all ages with any clinical presentation of Lyme disease.

The key population exclusion criterion was:

People with other tick-borne infections.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies, conference abstracts and studies not in English were excluded.

Type of Studies

Randomised trials, non-randomised intervention studies, and other observational studies (including diagnostic and epidemiological studies) were included in the evidence reviews as appropriate.

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that can produce an unbiased estimate of the intervention effects. If there was limited evidence from RCTs, well-conducted non-randomised studies were included. Please refer to the review protocols in each evidence report for full details on the

study design of studies selected for each review question.

For diagnostic accuracy review questions, cross-sectional studies and retrospective studies were considered the most appropriate study design. Case-control studies were also included due to a general lack of evidence from cross-sectional and retrospective studies. For epidemiological review questions, any studies reporting an incidence or prevalence estimate or a transmission risk estimate for Lyme disease were included.

Where data from non-randomised studies were included, the results for each outcome were presented separately for each study or meta-analysed if appropriate.

Identifying and Analysing Evidence of Cost-effectiveness

Literature Review

The health economists:

Identified potentially relevant studies for each review question from the health economic search results by reviewing titles and abstracts. Full papers were then obtained.

Reviewed full papers against prespecified inclusion and exclusion criteria to identify relevant studies.

Inclusion and Exclusion Criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as health economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Studies published before 2001 and studies from non-Organisation for Economic Co-operation and Development (OECD) countries or the US were also excluded, on the basis that the applicability of such studies to the present UK NHS context is likely to be too low for them to be helpful for decision-making.

Remaining health economic studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, it is noted in the relevant evidence report. However, in this guideline, no economic studies were excluded on the basis that more applicable evidence was available.

For more details about the assessment of applicability and methodological quality see Table 9 in the "Methods" document (see the "Availability of Companion Documents" field) and the economic evaluation checklist (Appendix H of the NICE guidelines manual) and the health economics review protocol, which can be found in each of the evidence reports.

When no relevant health economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the committee to inform the possible economic implications of the recommendations.

Number of Source Documents

See Appendix C and Appendix F in each evidence report (see the "Availability of Companion Documents" field) for clinical and health economic evidence selection, respectively.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Overall Quality of Outcome Evidence in Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Level	Description
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Guideline Centre on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the evidence reviews for this guidance.

Analysing Evidence of Effectiveness

Research fellows conducted the tasks listed below:

Critically appraised relevant studies using the appropriate study design checklist as specified in the NICE guidelines manual (see the "Availability of Companion Documents" field). Qualitative studies were critically appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Confidence in the Evidence from Reviews of Qualitative research (CERQual) approach for rating confidence in the body of evidence as a whole and using a National Guideline Centre checklist for the methodological limitations section of the quality assessment.

Epidemiological studies were critically appraised using an adapted version of The Joanna Briggs Institute critical appraisal checklist for studies reporting incidence and prevalence data.

Extracted key information about interventional study methods and results using 'Evibase', National Guideline Centre's purpose-built software. Evibase produces summary evidence tables, including critical appraisal ratings. Key information about non-interventional study methods and results was manually extracted onto standard evidence tables and critically appraised separately (evidence tables are included in an appendix to each of the evidence reports).

Generated summaries of the evidence by outcome. Outcome data were combined, analysed and reported according to study design:

Randomised data were meta-analysed where appropriate and reported in GRADE profile tables. Data from non-randomised studies were presented as a range of values in GRADE profile tables or meta-analysed if appropriate.

Diagnostic data studies: coupled sensitivity and specificity values were summarised in forest plots. No meta-analyses were undertaken for the 3 review questions on diagnostic tests. This was due to heterogeneity in terms of different types of diagnostic tests and their

manufacturers, differences in how the tests were performed and their results were analysed, and differences in the study populations analysed. Where meta-analysis was performed for the review question on signs and symptoms, coupled sensitivity and specificity values were also presented on summary receiver operating characteristic (sROC) plots along with the results of the meta-analysis (the summary sensitivity and specificity point and 95% confidence region) and the summary curve. Where evidence was not meta-analysed, because studies differed in population or outcome, then no alternative pooling strategies were carried out on the basis that such pooling would have little meaning. Results from single studies were presented.

Qualitative data were synthesised across studies and presented as summary statements with accompanying GRADE CERQual ratings for each review finding.

Epidemiological data were presented as individual values or as a range of values. No meta-analyses were undertaken because the majority of studies based their incidence calculations on samples tested at reference laboratories in England and Scotland. As such, meta-analysing the individual results would mean that samples could be counted multiple times.

All of the evidence reviews were quality assured by a senior research fellow. This included checking:

- Papers were included or excluded appropriately

- A sample of the data extractions

- Correct methods were used to synthesise data

- A sample of the risk of bias assessments.

Methods of Combining Clinical Studies

Refer to Section 2.3.3 in the "Methods" document for data synthesis for intervention reviews, diagnostic test accuracy reviews, qualitative study reviews, and epidemiological review studies.

Appraising the Quality of Evidence by Outcomes

Intervention Reviews

The evidence for outcomes from the included randomised controlled trials (RCTs) and, where appropriate, non-randomised intervention studies, were evaluated and presented using an adaptation of the 'GRADE toolbox' developed by the international GRADE working group (<http://www.gradeworkinggroup.org/>
). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results.

Each outcome was first examined for each of the quality elements listed and defined in Table 2 in the "Methods" document.

Details of how the 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) were appraised for each outcome are given in Sections 2.3.4.1.1 to 2.3.4.1.4 of the "Methods" document. Publication or other bias was only taken into consideration in the quality assessment if it was apparent.

Diagnostic Studies

Risk of bias and indirectness of evidence for diagnostic data were evaluated by study using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklists (see Appendix H in the NICE guidelines manual 2014). Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS-2 consists of 4 domains (see Figure 3 in the "Methods" document):

- Patient selection

- Index test

- Reference standard

- Flow and timing.

Details of how inconsistency and imprecision were appraised for each outcome are given in Sections 2.3.4.2.1 to 2.3.4.1.2 of the "Methods" document.

Qualitative Reviews

Review findings from the included qualitative studies were evaluated and presented using the CERQual Approach developed by the GRADE-CERQual Project Group, a subgroup of the GRADE Working Group.

The CERQual Approach assesses the extent to which a review finding is a reasonable representation of the phenomenon of interest (the focus of the review question). Each review finding was assessed for each of the 4 quality elements listed and defined below in Table 5 in the "Methods" document.

Details of how the 4 quality elements (methodological limitations, coherence, relevance and adequacy) were appraised for each review finding are given in Sections 2.3.4.3.1 to 2.3.4.3.4 of the "Methods" document.

Epidemiological Reviews

In the absence of any established study limitations checklists for epidemiological reviews, risk of bias and indirectness of evidence were assessed using an adapted version of a checklist for incidence and prevalence studies published by The Joanna Briggs Institute. The published checklist was adapted for the purpose of this guideline because the sections on an adequate sample size and response rate were not applicable for this guideline, since the reviews on the incidence and transmission of Lyme disease used clinical data, such as serological samples tested, to establish a risk estimate. Response rates to surveys, such as a general census, or drop-out rates were therefore not applicable.

Each question has to be answered with 'yes', 'no', 'unclear' or 'not applicable'. Based on the quality elements described in Table 7 in the "Methods" document, studies were given a Low, Moderate, or High risk of bias.

Inconsistency was not assessed as no meta-analyses or other pooling strategies were performed. Imprecision could not be assessed because the majority of included studies did not provide any confidence intervals (CIs) for the incidence and transmission estimates.

Assessing Clinical Importance

The committee assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of clinical benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies, which was standardised across the reviews. The committee considered for dichotomised outcomes in the intervention reviews that if at least 100 more participants per 1,000 (10%) achieved the outcome of interest in the intervention group compared to the comparison group for a positive outcome then this intervention was considered beneficial. The same point estimate but in the opposite direction applied for a negative outcome. For adverse events, 50 events or more per 1,000 (5%) represented clinical harm. For continuous outcomes if the mean difference was greater than the minimally important difference (MID), then this represented a clinical benefit or harm.

Established MIDs were found in the literature for the outcome SF-36 and the values used for imprecision and clinical importance are provided in Table 8 in the "Methods" document. For all other outcome, the default approach was used.

This assessment was carried out by the committee for each critical outcome, and an evidence summary table was produced to compile the committee's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

Clinical Evidence Statements

Clinical evidence statements are summary statements that are included in each evidence report, and which summarise the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence

statements are presented by outcome and encompass the following key features of the evidence:

- The number of studies and the number of participants for a particular outcome.

- An indication of the direction of clinical importance (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments).

- A description of the overall quality of the evidence (GRADE overall quality).

Analysing Evidence of Cost-effectiveness

The committee is required to make decisions based on the best available evidence of both clinical effectiveness and cost-effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost-effectiveness') rather than the total implementation cost. However, the committee will also need to be increasingly confident in the cost-effectiveness of a recommendation as the cost of implementation increases. Therefore, the committee may require more robust evidence on the effectiveness and cost-effectiveness of any recommendations that are expected to have a substantial impact on resources; any uncertainties must be offset by a compelling argument in favour of the recommendation. The cost impact or savings potential of a recommendation should not be the sole reason for the committee's decision.

Health economic evidence was sought relating to the key clinical issues being addressed in the guideline. Health economists:

- Undertook a systematic review of the published economic literature.

- Undertook new health economic exploratory analysis in priority areas.

Literature Review

The health economists:

- Critically appraised relevant studies using economic evaluations checklists as specified in the NICE guidelines manual.

- Extracted key information about the studies' methods and results into health economic evidence tables (which can be found in appendices to the relevant evidence reports).

- Generated summaries of the evidence in NICE health economic evidence profile tables (included in the relevant evidence report for each review question) – see below for details.

NICE Health Economic Evidence Profiles

NICE health economic evidence profile tables were used to summarise cost and cost-effectiveness estimates for the included health economic studies in each evidence review report. The health economic evidence profile shows an assessment of applicability and methodological quality for each economic study, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from the NICE guidelines manual. It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio (ICER) for the base-case analysis in the study, as well as information about the assessment of uncertainty in the analysis. See Table 9 in the "Methods" document for more details.

When a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.

Undertaking New Health Economic Analysis

As well as reviewing the published health economic literature for each review question, as described above, new health economic analysis was undertaken by the health economist in selected areas. The committee agreed on the priority areas for new analysis after formation of the review questions and consideration of the existing health economic evidence.

The committee identified diagnosis as the highest priority area for original health economic modelling.

The committee identified diagnosis as a high priority because it affects the largest number of people in the guideline (that is, all those tested), there are a number of uncertainties over the most appropriate approach to testing, and there are no includable health economic analyses to aid consideration of cost-effectiveness.

Current practice in the NHS is a 2-tier testing strategy; an 'initial' test (an enzyme-linked immunosorbent assay [ELISA]) followed by 'confirmatory' test (an immunoblot) for those with a positive or equivocal initial test result. The committee were interested to establish if the current 2-tier testing was cost effective compared to a single test. They also highlighted uncertainty as to whether other tests, not currently being used in the NHS, may be of value. Based on the review of the clinical evidence identified, the committee agreed to make recommendations that reflected current practice (as described above) with some exceptions, which are discussed in more detail in Evidence Review C. A full cost-utility analysis to establish whether or not the current 2-tier testing approach is cost effective compared to initial testing only was considered inappropriate as there is too much uncertainty around model inputs and too many tenuous assumptions would be required. As a result, a simple exploratory analysis was conducted to justify the additional cost of 2-tier testing (ELISA including C6 immunoglobulin M [IgM] and immunoglobulin G [IgG] followed by confirmatory immunoblot if ELISA is positive) over initial testing only (ELISA including C6 IgM and IgG) in people with suspected Lyme disease. More detail on the rationale for this approach and the methodology and results are available in Appendix H of Evidence Review C.

The following general principles were adhered to in developing the analysis:

- Methods were consistent with the NICE reference case for interventions with health outcomes in NHS settings, although this analysis was restricted to costs only and so QALYs were not used.

- Furthermore, a PSA was not deemed useful for this exploratory analysis. Further detail is provided in the full write up.

- The committee was involved in the selection of inputs and interpretation of the results.

- Inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.

- Inputs and assumptions were reported fully and transparently.

- The results were subject to sensitivity analysis and limitations were discussed.

- The analysis was peer-reviewed by another health economist at the National Guideline Centre.

Full methods and results of the exploratory analysis comparing 2-tier testing to single testing for Lyme disease are described in Evidence Review C.

Cost-effectiveness Criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that committees should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective (given that the estimate was considered plausible) if either of the following criteria applied:

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or

- The intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in 'The committee's discussion of the evidence' section of the relevant evidence report, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.

When QALYs or life-years-gained are not used in the analysis, results are difficult to interpret unless 1 strategy dominates the others with respect to every relevant health outcome and cost.

In the Absence of Health Economic Evidence

When no relevant published health economic studies were found, and a new analysis was not prioritised, the committee made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the review of clinical effectiveness evidence.

The UK NHS costs reported in the guideline are those that were presented to the committee and were correct at the time recommendations were drafted. They may have changed subsequently before the time of publication. However, the committee has no reason to believe they have changed substantially.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Guideline Centre on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the general methods and the evidence reports used to produce this guidance.

Who Developed This Guideline?

A multidisciplinary guideline committee comprising health professionals and researchers as well as lay members developed this guideline (see the list of guideline committee members and the acknowledgements).

The committee was convened by the National Guideline Centre and chaired by Saul Faust in accordance with guidance from NICE. The group met approximately every 4 to 6 weeks during the development of the guideline. Staff from the NGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers (research fellows), health economists and information specialists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the committee.

Developing Recommendations

Over the course of the guideline development process, the committee was presented with:

- Summaries of clinical and health economic evidence and quality (as presented in evidence reports A-N).

- Evidence tables of the clinical and health economic evidence reviewed from the literature. All evidence tables can be found in appendices to the relevant evidence reports.

- Forest plots and summary receiver operating characteristic (ROC) curves (in appendices to the relevant evidence reports).

- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (in a separate economic analysis report).

Recommendations were drafted based on the committee's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net clinical benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the committee took into account the clinical benefits and harms when 1 intervention was compared with another. The assessment of net clinical benefit was moderated by the importance placed on the outcomes (the committee's values and preferences), and the confidence the committee had in the evidence

(evidence quality). Secondly, the committee assessed whether the net clinical benefit justified any differences in costs between the alternative interventions.

When clinical and health economic evidence was of poor quality, conflicting or absent, the committee drafted recommendations based on its expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the committee. The committee also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see section 2.5.1 in the "Methods" document).

The committee considered the appropriate 'strength' of each recommendation. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the committee believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the committee has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances, the recommendation is generally weaker although it may be possible to make stronger recommendations about specific groups of patients. The committee focused on the following factors in agreeing the wording of the recommendations:

- The actions health professionals need to take.

- The information readers need to know.

- The strength of the recommendation (for example, the word 'offer' was used for strong recommendations and 'consider' for weaker recommendations).

- The involvement of patients (and their carers if needed) in decisions on treatment and care.

- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see section 9.2 in the NICE guidelines manual [see the "Availability of Companion Documents" field]).

The main considerations specific to each recommendation are outlined in 'The committee's discussion of the evidence' section within each evidence report.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Committee (GC) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GC is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, National Institute for Health and Care Excellence (NICE) expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision.

Interventions That Must (or Must Not) Be Used

The GC usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally they use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GC uses 'offer' (and similar words such as 'refer' or 'advise') when they are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. They use similar forms of words (for example, 'Do not offer...') when they are confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GC uses 'consider' when they are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Cost Analysis

Refer to the "Cost-effectiveness and Resource Use" sections in each evidence report (see the "Availability of Companion Documents" field).

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Validation Process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the National Institute for Health and Care Excellence (NICE) Web site.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The type of evidence supporting each review area is detailed in the individual evidence reports (see the "Availability of Companion Documents" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Raising awareness of Lyme disease reduces the possibility that people with Lyme disease are overlooked or not adequately assessed and diagnosed for Lyme disease. Receiving appropriate treatment provides the best chance of reducing morbidity.

- The benefits of testing include improved confidence in the diagnosis in positive cases and avoidance of inappropriate treatment, delay in investigation of other causes and potential attribution of future symptoms to Lyme disease in negative cases.
- The committee agreed that the emphasis on higher doses and 3- or 4-week treatment courses in this guideline should reduce treatment failure but recognised that this can still occur.

Refer to the "Benefits and harms" sections in the individual evidence reports (see the "Availability of Companion Documents" field) for details about benefits of specific interventions.

Potential Harms

- The diagnostic evidence showed that where accuracy data was available all symptoms had high specificity and low sensitivity, which means that false positives are few but false negatives are high. As a result, few people who do not have Lyme disease are identified as having Lyme disease, but many people with Lyme disease will be missed.
- For each person, the benefits of testing should be weighed against the potential risks of causing additional worry to the person and a localised infection developing to a disseminated one. In some cases, it may be appropriate to give a 'possible' or 'probable' diagnosis of Lyme disease and treat accordingly while waiting for test results to become available.
- The committee considered the different adverse event profiles of different antimicrobials and whether these may impact the costs of managing Lyme disease as well as their impact on the patient's quality of life. Doxycycline adverse events, for example, include photosensitivity, nausea and vomiting. It was also noted that a rare side effect of azithromycin is QT prolongation. In practice, if a person experiences any of these adverse events, these would be managed by switching to another antimicrobial and therefore the cost to the National Health Service (NHS) would be a consultation with a general physician (GP) and additional antimicrobials.

Refer to the "Benefits and harms" sections in the individual evidence reports (see the "Availability of Companion Documents" field) for details about harms of specific interventions.

Contraindications

Contraindications

- At the time of publication (April 2018), doxycycline did not have a UK marketing authorisation for this indication in children under 12 years and is contraindicated in this age group because of side effects, such as teeth staining. The use of doxycycline for children aged 9 years and above in infections where doxycycline is considered first line in adult practice is accepted specialist practice.
- The committee noted that azithromycin should not be used to treat people with cardiac abnormalities because of its effect on the QT interval.

Qualifying Statements

Qualifying Statements

- The recommendations in this guideline represent the view of the National Institute for Health and Care Excellence (NICE), arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in

consultation with them and their families and carers or guardian.

- Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.
- Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

Implementation of the Guideline

Description of Implementation Strategy

The National Institute for Health and Care Excellence (NICE) has produced [tools and resources](#) (see also the "Availability of Companion Documents" field) to help put this guideline into practice. For general help and advice on putting NICE guidelines into practice, see [putting recommendations into practice: quick tips](#) .

Implementation Tools

Clinical Algorithm

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2018 Apr 11

Guideline Developer(s)

National Guideline Centre - National Government Agency [Non-U.S.]

Source(s) of Funding

The National Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

Guideline Committee

Guideline Committee

Composition of Group That Authored the Guideline

Guideline Committee Members: Saul Faust (*Chair*), Professor of Paediatric Immunology & Infectious Diseases & Director, NIHR Wellcome Trust Clinical Research Facility, University of Southampton; Srini Bandi, Consultant Paediatrician, Leicester Royal Infirmary; Stephen Barton, Lay member; Nick Beeching, Senior Lecturer and Honorary Consultant in Infectious Diseases, Liverpool School of Tropical Medicine and Tropical and Infectious Disease Unit, Royal Liverpool University Hospital; Robin Brittain-Long, Consultant Physician, Acute Medicine and Infectious Diseases, Aberdeen Royal Infirmary; Tim Brooks, Clinical Services Director, Microbiologist, Public Health England; Scott Hackett, Consultant in Paediatric Allergy, Immunology and Infectious Diseases, Birmingham Heartlands Hospital; Cheryl Hemingway, Consultant Paediatric Neurologist, Great Ormond Street Children's Hospital; Neil Hopkinson, Consultant Rheumatologist, Royal Bournemouth & Christchurch Hospitals; Veronica Hughes, Lay member; Stella Huyshe-Shires, Lay member; Melissa McCullough, Lay member; Caroline Rayment, General Practitioner, Grange Park Surgery; David Stephens, Portfolio General Practitioner; Nick Davies, Consultant Neurologist, Chelsea & Westminster Hospital (*Co-opted member – Adult Neurologist*); Kieran Hand, Consultant Pharmacist – Anti-infectives, University Hospital Southampton NHS Foundation Trust (*Co-opted member – Pharmacist*)

Financial Disclosures/Conflicts of Interest

At the start of the guideline development process, all committee members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent committee meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in the declaration of interest register for this guideline published on the [National Institute for Health and Care](#)

Excellence (NICE) Web site .

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the [National Institute for Health and Care Excellence \(NICE\) Web site](#)

. Also available for download in ePub or eBook formats from the [NICE Web site](#)
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Availability of Companion Documents

The following are available:

Lyme disease. Evidence reviews. London (UK): National Institute for Health and Care Excellence (NICE); 2018 Apr. (NICE guideline; no. 95). Available from the [National Institute of Health and Care Excellence \(NICE\) Web site](#) .

Lyme disease. Methods. London (UK): National Institute for Health and Care Excellence (NICE); 2018 Apr. 51 p. (NICE guideline; no. 95). Available from the [NICE Web site](#) .

Lyme disease. Acknowledgements. London (UK): National Institute for Health and Care Excellence (NICE); 2018 Apr. 6 p. (NICE guideline; no. 95). Available from the [NICE Web site](#)
.

Membership of lyme disease guideline committee. London (UK): National Institute for Health and Care Excellence (NICE); 2018 Apr. 13 p. (NICE guideline; no. 95). Available from the [NICE Web site](#)
.

Lyme disease. Baseline assessment tool. London (UK): National Institute for Health and Care Excellence (NICE); 2018 Apr. (NICE guideline; no. 95). Available from the [NICE Web site](#)
.

Lyme disease. Resource impact statement. London (UK): National Institute for Health and Care Excellence (NICE); 2018 Apr. (NICE guideline; no. 95). Available from the [NICE Web site](#)
.

Developing NICE guidelines: the manual. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. Available from the [NICE Web site](#) .

In addition, Lyme disease rash images are available on the [NICE Web site](#) .

Patient Resources

The following is available:

Lyme disease. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2018 Apr. (NICE guideline; no. 95). Available from the [National Institute of Health and Care Excellence \(NICE\) Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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